To the editor:

Phase IB study of cabozantinib in patients with relapsed and/or refractory multiple myeloma

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Despite the introduction of proteasome inhibitors and immunomodulatory drugs followed by autologous stem cell transplant, most patients with multiple myeloma (MM) will have disease recurrence after primary therapy. Thus, agents with different mechanisms of action and different targets need to be explored. We conducted a phase 1B study of cabozantinib in patients with relapsed and/or refractory MM (NCT01866293). Cabozantinib is a small-molecule inhibitor of multiple receptor tyrosine kinases implicated in tumor growth and neoangiogenesis. The primary targets of cabozantinib are hepatocyte growth factor (HGF) receptor protein, vascular endothelial growth factor receptor 2, and RET.[1] HGF and HGF receptor protein (MET) have been implicated in myeloma pathogenesis based on the observation that elevated HGF levels are associated with worse prognosis[2-4] and lack of response to chemotherapy.[5,6] In addition, MM cells express HGF, creating a putative autocrine HGF/MET loop.[7-9] In vitro models demonstrated myeloma cell growth inhibition through MET or HGF inhibition.[10,11]

Here, we report our experience with single-agent cabozantinib. Two phase 1 studies were conducted, one at Memorial Sloan-Kettering Cancer Center (MSK; NCT01866293) and one at Massachusetts General Hospital Cancer Center (MGH; NCT01582295). The design of the studies was the same, as was the starting dose. The research studies were approved by the MSK and MGH institutional review boards, and all participants gave written informed consent. Eligible patients received cabozantinib orally as a tablet daily on a 28-day cycle. The trials had a standard 3-by-3 dose-escalation design, with 3 daily dose levels (dose level −1, 20 mg; dose level 1, 40 mg; and dose level 2, 60 mg). Patients were assessed for safety every 2 weeks during the first 3 cycles at MSK and weekly at MGH. Myeloma response was assessed by International Myeloma Working Group criteria after each cycle. The dose-limiting toxicity (DLT) evaluation period was 6 and 4 weeks at MSK and MGH, respectively. Major eligibility criteria included MM that was relapsed or refractory after therapy with at least 1 immunomodulatory drug and at least 1 proteasome inhibitor, as well as adequate bone marrow reserve (defined as ANC $\geq$1500/mm^3 [MSK] or $\geq$1000 [MGH], platelets $\geq$50 000/mm^3, bilirubin $\leq$1.5 times the upper limit of normal, and serum creatinine $\leq$ 1.5 times the upper limit of normal or calculated creatinine clearance $\geq$50 mL/min [MSK] or $\geq$ 45 mL/min [MGH]). Patients requiring therapeutic anticoagulation or with a recent history of pulmonary or gastrointestinal bleed or with cavitating pulmonary lesions or major surgery were excluded.

Nine patients received treatment with cabozantinib at MSK and 3 at MGH. Patient characteristics are as shown in Table 1. The initial starting dose was 40 mg daily. In the initial cohort of 3 patients at MSK, 1 DLT was observed (congestive heart failure in a patient with a history of congestive heart failure). Therefore, 3 additional patients were treated at the 40 mg dose level. Because no further DLT was observed at the 40 mg dose level, 3 patients were treated at dose level II (60 mg daily). Three patients were treated at the initial dose level of 40 mg at MGH. No DLTs were observed.

The median time on therapy was 61 days (range, 14-128). Best responses for all patients were 1 minimal response, 8 stable disease, and 2 progression of disease. One patient was inevaluable for response, having experienced a DLT prior to completing the first cycle of therapy. There were 2 serious adverse events (AEs; 1 grade 2 congestive heart failure and 1 grade 3 PNA) felt to be possibly cabozantinib related. Most other nonhematologic AEs were primarily gastrointestinal and were mostly grade 1 or 2 and included diarrhea (67%, grade 3 in 1 patient), abdominal pain/bloating (25%), nausea/anorexia (50%), dysgeusia (17%), alanine aminotransferase/aspartate aminotransferase elevation (89% and 58%, respectively), and lipase/amylase elevation (42% and 25%, respectively). Hyperglycemia (75%, grade 3 in 2 patients), hypocalcemia (42%), hypomagnesemia (33%), and hypophosphatemia (33%, grade 3 in 1 patient) were also commonly noted. Less frequently seen grade 1/2 treatment-emergent AEs thought to be possibly due to cabozantinib included dyspnea (42%), hoarseness (25%), palmar-plantar erythrodysesthesia syndrome (17%), hypopigmentation (17%), and grade 2 neuropathy in 1 patient. Grade 3 hematologic AEs were anemia (2 patients), lymphopenia (4 patients), neutropenia (2 patients, grade 4 in 1 patient).

The reasons for discontinuation of therapy were DLT in 1 patient, progression of disease in 7 patients, and withdrawal of consent in 4 patients. MTD was not reached. However, given the lack of activity, the

Table 1. Patient characteristics (n = 12)

	n (%)
Median age (range), y	64 (53-76)
Female	7 (58%)
High-risk cytogenetics	6 (50%)
Median prior lines of therapy (range)	3 (1-7)
Prior proteasome inhibitor	12 (100%)
Prior carfilzomib	6 (50%)
Prior IMiD	12 (100%)
Prior pomalidomide	2 (17%)
Double refractory (to PI and IMiD)	7 (58%)
Prior high-dose melphalan with stem cell rescue	9 (75%)

IMiD, immunomodulatory drug; PI, proteasome inhibitor.

fact that 4 patients withdrew consent due to toxicities, and considering the impact of the grade 1-2 toxicities on our patients' quality of life, it was thought that exploring higher dose levels was not warranted.

We conclude that cabozantinib does not have significant single-agent activity in patients with relapsed and/or refractory MM. HGF levels at the time of study entry were not available in these patients; therefore, this study does not exclude the possibility that cabozantinib may have activity in myeloma patients with higher levels of HGF or where disease is driven by HGF.

*N.L. and A.J.Y. contributed equally to this study.

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References

1. Yakes FM, Chen J, Tan J, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther.* 2011;10(12):2298-2308.
2. Seidel C, Børset M, Turesson I, Abildgaard N, Sundan A, Waage A; The Nordic Myeloma Study Group. Elevated serum concentrations of hepatocyte growth factor in patients with multiple myeloma. *Blood.* 1998; 91(3):806-812.
3. Seidel C, Lenhoff S, Brabrand S, et al; Nordic Myeloma Study Group. Hepatocyte growth factor in myeloma patients treated with high-dose chemotherapy. *Br J Haematol.* 2002;119(3):672-676.
4. Wader KF, Fagerli UM, Holt RU, et al. Elevated serum concentrations of activated hepatocyte growth factor activator in patients with multiple myeloma. *Eur J Haematol.* 2008;81(5):380-383.
5. Pour L, Svachova H, Adam Z, et al. Levels of angiogenic factors in patients with multiple myeloma correlate with treatment response. *Ann Hematol.* 2010;89(4): 385-389.
6. Pour L, Svachova H, Adam Z, et al. Pretreatment hepatocyte growth factor and thrombospondin-1 levels predict response to high-dose chemotherapy for multiple myeloma. *Neoplasma.* 2010;57(1):29-34.
7. Choi Y, Zhang J, Murga C, et al. PTEN, but not SHIP and SHIP2, suppresses the PI3K/Akt pathway and induces growth inhibition and apoptosis of myeloma cells. *Oncogene.* 2002;21(34):5289-5300.
8. Tjin EP, Derksen PW, Kataoka H, Spaargaren M, Pals ST. Multiple myeloma cells catalyze hepatocyte growth factor (HGF) activation by secreting the serine protease HGF-activator. *Blood.* 2004;104(7):2172-2175.
9. Wader KF, Fagerli UM, Børset M, et al. Immunohistochemical analysis of hepatocyte growth factor and c-Met in plasma cell disease. *Histopathology.* 2012;60(3):443-451.
10. Hov H, Holt RU, Rø TB, et al. A selective c-met inhibitor blocks an autocrine hepatocyte growth factor growth loop in ANBL-6 cells and prevents migration and adhesion of myeloma cells. *Clin Cancer Res.* 2004;10(19):6686-6694.
11. Phillip CJ, Stellrecht CM, Nimmanapalli R, Gandhi V. Targeting MET transcription as a therapeutic strategy in multiple myeloma. *Cancer Chemother Pharmacol.* 2009;63(4):587-597.

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To the editor:

Ibrutinib responsive central nervous system involvement in chronic lymphocytic leukemia

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Central nervous system involvement (CNSi) is a rare complication in chronic lymphocytic leukemia (CLL).[1-3] Neither prognostic factors nor consensual therapeutic management guidelines are available. Multiple therapies targeting either the CNS or CLL have been used with variable results in terms of rate and duration of response.[4,5] Outcome after CNS treatment is not established and controversies persist about the need to control the systemic CLL.

Ibrutinib is the first in a class of US Food and Drug Administration (FDA)–approved Bruton tyrosine kinase inhibitor that acts by blocking B-cell antigen receptor signaling and changing the tumor microenvironment,[6] thereby reducing malignant proliferation of B cells and inducing apoptosis.[6-8] It is indicated in relapsed/refractory and in treatment-naïve 17p-deleted CLL.[9] Here we present, on behalf of the French Innovative Leukemia Organization, the first report of 4 consecutive cases of CNSi in CLL successfully treated with ibrutinib monotherapy.

We retrospectively collected clinical, biologic, and radiologic data of 4 CLL patients diagnosed with specific CNSi between August 2012 and February 2015, and treated with ibrutinib. The study was approved by the Institutional Review Board and conducted according to the Declaration of Helsinki. All patients met the International Workshop on CLL (iwCLL) diagnosis criteria for CLL. CNSi was defined by positive cerebrospinal fluid (CSF) cytology and flow cytometry with or without image evidence of brain tumor. Ibrutinib treatment was administered at a standard dose (420 mg/d) as a single agent. Response assessment was based on disappearance of clinical symptoms, CSF clearance, and neuroimaging when applicable. Response for CLL was assessed according to the iwCLL guidelines.[10]

Patients and disease characteristics at CNSi diagnosis are summarized in Table 1. CNSi occurred within a median of 106 months (range, 0-207) after the diagnosis of CLL. Two patients had progressive hematologic disease and 3 patients were heavily pretreated at the time of CNSi. Median lymphocytosis was 15 G/L (range, 0.9-245). Cytogenetic analysis showed 17p deletion in 3 patients, trisomy 12 in 2 patients, and a complex karyotype in 2 patients. Neurologic symptoms were heterogeneous and multifocal. CNSi diagnosis was late in 2 patients. Diagnosis was established on CSF analysis: all patients had leptomeningeal involvement. Median CSF cellularity was 30 μL^{-1} (range, 22-231) with lymphocytic predominance (>90%). Percentage of CLL cells detected by immunophenotyping was highly heterogeneous